Chemical reactions in supercritical carbon dioxide: from laboratory to commercial plant†

Perspective

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The application of supercritical carbon dioxide in continuous, fixed bed reactors has allowed the successful development of a variety of industrially viable synthetic transformations. The world's first, multi-reaction, supercritical flow reactor was commissioned in 2002 as a direct result of the successful collaboration between the Clean Technology Group at the University of Nottingham and the fine chemicals manufacturer, Thomas Swan & Co. Ltd. We highlight the development of this project from laboratory to plant scale, particularly in the context of the hydrogenation of isophorone. Phase data for the system; isophorone + H_2 + CO_2, are presented for the first time. Overall, we present a progress report about an on-going Green Chemistry initiative that has successfully forged strong links between Industry and Academia.

Introduction

This is an unusual paper because it traces a project from simple experiments in the laboratory right up to the construction of a full scale plant capable of producing 1000 tons *per annum*. We believe that the story is important because a major aim of Green Chemistry is the implementation of new technologies on a large scale and, as yet, there are very few concrete examples of this aim being realised in practice.[1,2] The project is important for a second reason, namely that the plant itself is a large-scale Green Chemistry experiment and a rare example of a new technology being put to the test in public. Like all such projects, the full history is quite convoluted. Here we highlight only the most significant events.

The project involves chemical reactions in supercritical fluids (SCFs) which have been recognised for some time as possible replacements for environmentally less acceptable solvents.[2,3] In particular, supercritical CO_2 (scCO_2) has been used widely for extraction processes,[4] for example for the extraction of caffeine from coffee beans. The decaffeination of coffee is an outstanding example of a green technology that has largely supplanted earlier processes.[3,4] Most importantly, for this project, the pre-existence of a mature SCF extraction industry meant that most, if not all, of the equipment needed for chemistry in SCFs was already available well before the official start of the project in 1995. However, the project itself has a much longer history.

Originally, the motivation at Nottingham for carrying out chemical reactions under supercritical conditions was to provide a better route for the photochemical generation of unstable organometallic dihydrogen[5] and dinitrogen complexes such as those shown in Scheme 1.[6,7] One of the keys to the
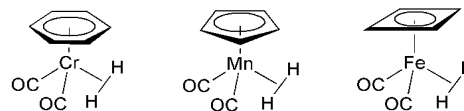
Scheme 1 Examples of unstable organometallic species prepared in supercritical fluids.[6]

success of this early work was the relatively high concentrations of H_2 and N_2 that could be readily achieved, because such gases

Representatives of the Nottingham/Thomas Swan team receiving the First Prize in the RSC 2002 Industrial Innovation Team Award from the RSC President, Sir Harry Kroto (centre), for their production scale process in supercritical carbon dioxide. (From the right) Dr Stephen Ross and Dr Murielle Sellin of Thomas Swan & Co., and Prof. Martyn Poliakoff and Dr Peter Licence of the University of Nottingham. The picture was taken immediately after Sir Harry had lightheartedly placed the upturned glass trophy as a helmet on Martyn's head!

Green Context

The success of Green Chemistry depends on the development of commercial scale processes based on the principles of green chemistry. The replacement of volatile organic solvents with more environmentally benign reaction media is one of the most exciting ideas to emerge from green chemistry research and here we can read about its successful transition to commercial production. The paper also demonstrates the potential value to both parties of academic industrial collaboration. *JHC*

are totally miscible with most SCFs. This concentration effect was later exploited for catalytic hydrogenation in SCFs by Noyori *et al.*[8] and others.[9]

We quickly extended our experiments to other SCF photo-reactions including C–H activation[10] and the synthesis of metal ethene complexes.[11] All of these reactions[6] were initially carried out in small spectroscopic cells (volume < 2 mL) which afforded little chance of isolating the 'unstable' products, even though many of them appeared to be surprisingly long-lived. This inspired us to devise miniature continuous reactors for carrying out such reactions on a preparative scale (see Fig. 1),[11–13] which subsequently enabled us to isolate a number of novel ethene and dihydrogen complexes, one of the few occasions when *new* compounds have been successfully isolated with the aid of SCFs.[6]
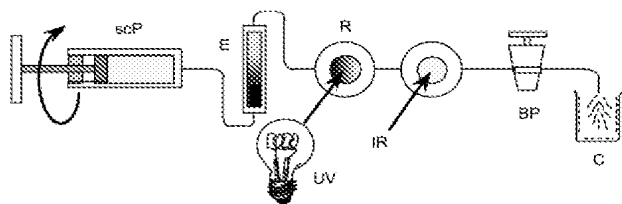
Fig. 1 Schematic view of a flow reactor[11] used for the isolation of Cr(CO)$_5$(C$_2$H$_4$) from supercritical C$_2$H$_4$, scC$_2$H$_4$. Parts are labelled as follows: scP, the scC$_2$H$_4$ pump; E, reservoir for solid Cr(CO)$_6$; R, the photolysis chamber for converting reactant to product; UV, photolysis lamp; IR, IR cell for optimising the reaction, BP, back-pressure regulator to release the pressure and to precipitate the product into the container C. (Note that, strictly, this is a batch type reactor being run in a flow mode because the reservoir E will eventually run out. In practise E could hold enough reactant for several experiments.)

Then came an unusual twist to the story. The work at Nottingham was included by David Bradley in his New Scientist feature article[14] on SCFs entitled *'Solvents get the Big Squeeze'*. The article covered a number of applications of SCFs, ranging from the decaffeination of coffee[4] to the development of new reactions and polymerisation techniques.[15] Crucially to this project, it also included M. Poliakoff's semi-humorous vision of SCF chemistry in the future as being *'as simple as operating a drinks vending machine. The chemist will simply press a button and the machine will add the appropriate reagents to the supercritical CO$_2$ and pump the mixture into the reactor'*. This frivolous statement caught the eye of Professor Tom Swan OBE, owner of the fine chemicals manufacturer, Thomas Swan & Co. Ltd., who recognised the potential that such 'dial a chemical' technology could bring to his business. He was also attracted by scCO$_2$ as a cleaner solvent because, at that time, it was feared that all chlorinated solvents might be banned. He contacted Nottingham, nine months of discussions began, and a collaboration was set up.

The strategy

It was decided to target continuous hydrogenation in scCO$_2$ using heterogeneous catalysts. This built on existing Nottingham expertise[11,12] in constructing flow reactors involving H$_2$ and, if successful, would lead to a new capability for Thomas Swan & Co. Ltd. Heterogeneous rather than homogeneous catalysis was chosen because it was experimentally simpler and there were more obvious routes to scale up under high pressure conditions. The objectives were ambitious: to develop a technology for hydrogenating a wide range of organic function-alities, with high selectivity, and on *a scale equivalent to tons per annum in the laboratory*.

It rapidly became clear that a multidisciplinary team would be required including organic chemists, high pressure engineers and catalyst developers. Thus, links were formed, at an early

stage, with the German catalyst manufacturers, Degussa AG, who had experience of catalysis in SCFs,[16] and with Dr K.-H. Pickel whose company, NWA GmbH, specialises in the manufacture of high pressure SCF apparatus.[17,18] Finally, a German post-doctoral researcher, Dr Martin Hitzler, was recruited to co-ordinate the research efforts.

Proof of concept

The project started in November 1995. The first reaction involved the hydrogenation of cyclohexene in supercritical CO$_2$, (Scheme 2). The results were striking, with a quantitative conversion being observed. The reaction proceeded with a very high linear hourly space velocity (LHSV) (*e.g.* 300 h^{-1} from a 5 mL reactor),[19,20] equivalent to a rate of 1200 mL per h or 7.5 tons *per annum*.
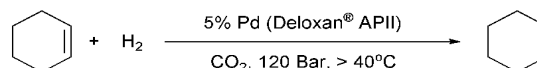
Scheme 2 The hydrogenation of cyclohexene under supercritical conditions, the reaction proceeded quantitatively with a very high LHSV (*e.g.* 300 h^{-1} from a 5 mL reactor).

These results complemented those of Härröd and co-workers who were working on the hydrogenation of oleochemicals in supercritical propane.[9,21] A detailed investigation at Nottingham into the hydrogenation of acetophenone (Scheme 3),
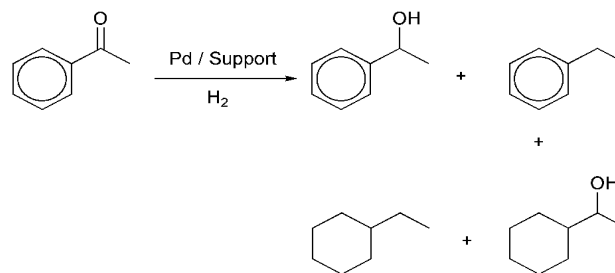
Scheme 3 The range of products obtained in the hydrogenation of acetophenone. Conditions could be chosen to maximize the yield of any one of these products.[19,20]

showed that scCO$_2$ allowed reaction conditions to be optimised very effectively to maximise the yield of particular hydro-genation products.[19] An interesting aspect was that the reactor delivered product free from any solvent. Thus, early in this project, all analysis was performed merely by diluting the product with deuterated solvent and running the ^{1}H NMR spectrum.[19,20] Later, the analysis was switched to more conventional methods, *e.g.* GC-FID, and GC-MS.

scCO$_2$ differs from conventional solvents in that its density is highly pressure dependent[4] and it is totally miscible with H$_2$ (see above). Furthermore, even if scCO$_2$ does not dissolve an organic liquid completely, CO$_2$ can dissolve into the liquid[22] causing it to expand considerably in volume, with a concomitant increase in the solubility of H$_2$ in the liquid phase. In general, our results suggested that, despite the unusual features of scCO$_2$ as a solvent, the overall selectivity of a given catalyst was not necessarily changed compared to its behaviour in conventional solvents but rather that conditions could be optimised more effectively in scCO$_2$.[23] The range of functionalities which could be hydrogenated in this way was quickly extended[19] and soon included those shown in Scheme 4. Most of these could be hydrogenated with high selectivity. There were some limita-tions, inherent to scCO$_2$, particularly the fact that aliphatic amines react with CO$_2$ to form insoluble carbamates,[3,4] which effectively terminate the reactions by precipitating and blocking the reactor.
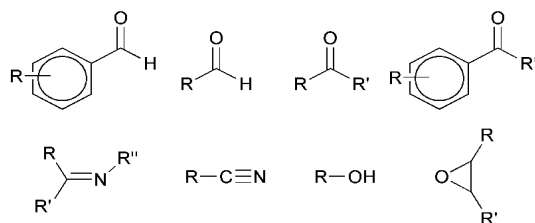
Scheme 4 Some of the functionalities that have been successfully hydrogenated under supercritical conditions as part of our project.[20]

Extending the chemistry

It was quickly realised that the SCF reactor was not restricted to hydrogenation reactions and could, in principle, be adapted to any type of solid or supported catalyst. Successful reactions included Friedel Crafts alkylation,[24] etherification,[25] hydroformylation[26] and base-catalysed transesterification.[27] The success of such reactions prompted Thomas Swan & Co. to set up their own SCF equipment in their research laboratories at Consett, UK. At the end of the first year, a PhD student, Fiona Smail was recruited to the project, Fig. 2. Further PhD students have been recruited annually.


Fig. 2 Picture of Dr F. R. Smail operating the first SCF reactor in Nottingham, (for a schematic view see Fig. 3). She joined the project in 1996 as a postgraduate student and, on completion of her PhD, joined Thomas Swan & Co. Ltd. where she is now Senior Research Chemist. In 2002, she won the CIA-SOCSA Innovation Prize for Young Chemists in recognition of her work in SCFs.
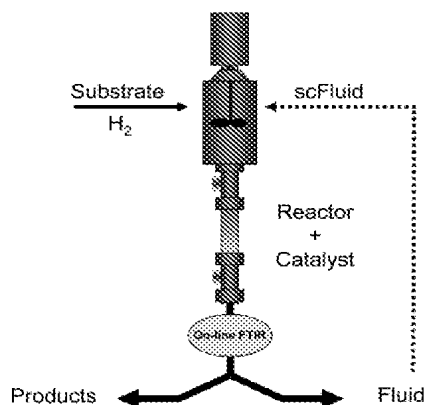
Fig. 3 Block diagram of the key components of the continuous reactor for hydrogenation of organic compounds at Nottingham.[19] scCO₂, H₂ and the organic substrate were mixed in a heated mixer. The mixture was then passed through a reactor containing a fixed bed catalyst (usually a supported noble metal). There was optional on-line FTIR monitoring before the product and CO₂ were separated by expansion. More recent reactors have used static rather mechanical premixers.

The development of a process

It was now important to identify a model compound, which could be used by the two laboratories, Nottingham and Thomas Swan & Co., as the basis for developing a viable SCF process. It was also important to choose a reaction of potential commercial interest where the ease of optimisation in scCO₂ could be exploited. The chosen reaction was the hydrogenation of isophorone to trimethylcyclohexanone (TMCH) (Scheme 5).[19] This reaction is a good model because the industrial end-
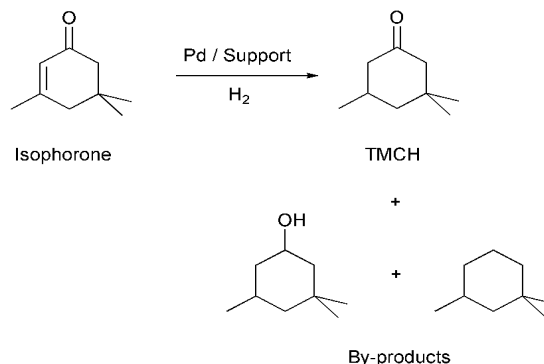
Scheme 5 Reaction scheme illustrating the range of products obtained in the hydrogenation of isophorone.

users require high purity product. The problem with conventional hydrogenation technologies is that they can easily lead to a mixture of TMCH and the over-hydrogenated by-products, trimethylcyclohexanol and trimethylcyclohexane.[28] All of these compounds, and isophorone itself, have similar boiling points, and the need to separate and purify TMCH from these mixtures adds greatly to both the cost and the environmental impact of the overall process.

This reaction was initially carried out on a laboratory-scale at Nottingham where it was found that conditions in scCO₂ could be adjusted to give quantitative conversion of isophorone to TMCH at a rate of up to 7 ml per min.[19] Clearly, if this process could be scaled up, one would eliminate the need for any purification steps following the hydrogenation. The work was then transferred to the laboratories at Thomas Swan & Co. where the industrial environment was better suited to investigating the feasibility of scale-up to a production scale. These investigations focussed particularly upon the choice of catalyst and catalyst lifetime.

Catalyst. The initial studies at Nottingham were carried out using catalysts supported on Deloxan®, a polysiloxane material from Degussa.[16] Deloxan® was found to be very durable and gave a good catalyst lifetime with up to 3 kg of product produced per gram of catalyst without significant loss of selectivity.[19] At this point, the decision was taken to commission a full-scale plant from the Swedish engineering company Chematur Engineering.

Then, there was a major setback. The Deloxan® range of catalysts was suddenly withdrawn from commercial production; an alternative source of catalysts was urgently required. Having screened a variety of catalysts, it was evident that a wide range of conversions and catalyst lifetimes could be obtained for a given noble metal, depending on the nature of the support. It was quickly recognised that the key criterion was the yield of TMCH *per g of Pd* rather than the yield *per g of catalyst*. These results supported previous work carried out by Hutchenson *et al.* in that Deloxan® outperformed most other catalysts with respect to conversion.[29] Eventually, alternative catalysts were identified that gave excellent catalyst life whilst retaining a level of conversion and product selectivity comparable to Deloxan®, see Table 1.

Table 1 Catalyst screening results for the selective hydrogenation of isophorone to trimethylcyclohexanone (TMCH)

Catalyst	Metal loading	kg TMCH/ g cat.	kg TMCH/ g Pd	Selectivity (%)
Deloxan®	Pd 5%	3.0	60	100
A	Pd 5%	0.4	8	91
B	Pd 2%	1.2	60	100
C	Pd 2%	1.1	55	>99
D	Pd 5%	3.0	60	98
E	Pd 2%	0.05	1	94

Reaction optimisation

Table 2 summarises the optimised conditions for the hydrogenation of isophorone in the laboratory. Particularly striking is the range of concentrations of isophorone which can be

Table 2 Optimised laboratory conditions for hydrogenation of isophorone to TMCH

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Reactor size	0.85 cm id, 25 cm long
Catalyst	2% Pd
Temperature	Inlet 56 °C
	Outlet 100 °C
Hydrogen	1.7–2.75 equivalents
Substrate feed	2–48 wt%

successfully reacted, 2–48 wt%. Supercritical reactions generally involve high pressures and considerable compression costs, in contravention of the 6th principle of Green Chemistry.[1,30] Clearly, maximising the concentration of isophorone will minimise the energy requirements of the process. At the same time, working with such high concentrations raises the whole issue of phase behaviour in the reaction mixture.

Phase behaviour. Considerable scientific argument has revolved around the question of whether supercritical hydrogenation reactions proceed faster and more efficiently in either a single or multiple phases; indeed conflicting reports have been published.[22,31–33] Much of this debate has revolved around the LHSV of a reaction, but this parameter only addresses part of the issue from an industrial perspective. Other important factors which have to be taken into account include catalyst lifetime, overall conversion and product selectivity as well as solvent compression costs. The situation has been at least partly resolved by a key paper by Nunes da Ponte and co-workers.[34] They have shown that biphasic reactions can sometimes be faster than monophasic ones, because the concentration of substrate (as opposed to H_2) is lower under monophasic conditions.

Because of the difficulty in measuring the high-pressure phase equilibrium of complex fluids, data on critical points and phase separations are scarce, especially for multi-component mixtures. Furthermore, the composition of a reaction mixture changes as the reaction proceeds.[35,36] Dissolving a substrate in a SCF mixture complicates the phase diagram of the system, when compared to that of a pure substance. Consequently, variations in temperature and pressure can have a much more pronounced effect on the phase behaviour of a fluid mixture than that of a pure substance.

Therefore we have undertaken a study[37] of the phase behaviour of four mixtures of varying composition, isophorone–CO_2–H_2 across six experimentally determined isotherms at 40, 60, 80, 100, 120 and 140 °C. This has established the boundary between the one and two phase regions of the phase diagram for this system; see Fig. 4.

The measurement of these phase equilibria clearly reveals that, for mixtures with a composition in excess of around 5% isophorone, quite substantial pressures and temperatures are
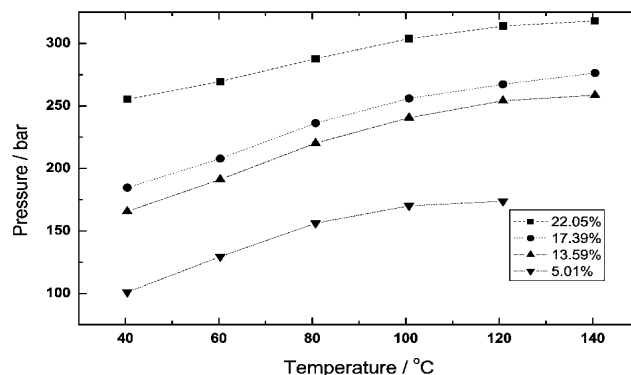

Fig. 4 Plot illustrating the experimentally determined phase boundaries of four mixtures of isophorone–CO_2–H_2 of varying composition. (Isophorone w/w 5–22 % w/w, molar ratio of isophorone : H_2 was fixed at 1 : 1.7).

required to render the system monophasic, a condition that has been reported to be essential for efficient and rapid hydrogenation.[32] By contrast, we have shown that this reaction can be carried out with excellent selectivity and conversion with as much as 50% isophorone in the reaction stream, conditions that are clearly not single phase. Furthermore, when conditions that facilitate single phase reactions are employed, a loss of desired product selectivity is observed as the high temperatures that are required often lead to the formation of unwanted side products.

The plant

Fig. 5 shows the schematic design of the Thomas Swan & Co. plant. It has a production capacity of ca. 100 kg per hour (1000 tons per annum). It therefore represents a ×400 scale-up of the laboratory reactor in terms of production.
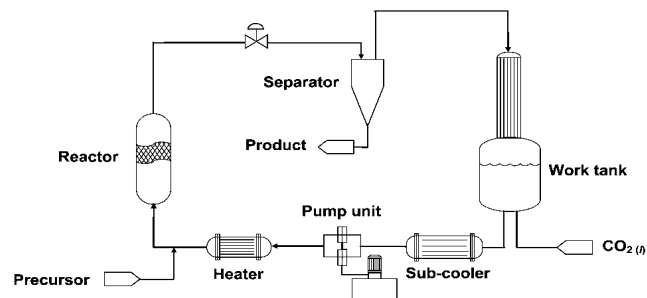
Fig. 5 Schematic flow diagram of the SCF plant at Thomas Swan & Co. Ltd., constructed by Chematur Engineering.

The plant is multi-purpose. The catalysts within the reactor can be changed to change the chemistry. A photograph of the actual reactors may be seen in Fig. 6. It is designed to work only with CO_2 as the SCF. (A new plant for reactions in supercritical propane is currently being built in Göteborg).[38] The Thomas Swan & Co. plant went on stream in June 2002.

The hydrogenation of isophorone was the first reaction to be run on the plant. The optimised conditions are shown in Table 3, and it is immediately clear that these conditions are very close to the optimised conditions in the laboratory, Table 2. If this transferability applies to other reactions, it will have considerable significance; reactions can be optimised in the laboratory and transferred almost directly to the plant.

Table 4 summarises the customer specifications for TMCH and an actual analysis of the raw product, direct from the plant. It can be seen that the product exceeded the specification in all five categories, although the acid value is only reached after residual CO_2 is removed by a brief application of vacuum. Thus,

Fig. 6 Photograph of the reactor array in the Thomas Swan & Co. SCF reactions plant.

Table 3 Optimised plant conditions for hydrogenation of isophorone to TMCH

Catalyst	2% Pd
Temperature	Isothermal 104–116 °C
Hydrogen	1.7 equivalents
Substrate feed	9–17 wt%

Table 4 Customer specification and product analysis for TMCH produced under supercritical conditions

Specification	Customer	SwanSCF
Colour (Hazen scale)	10 max	< 10
Assay (%)	99 min	99.4
Trimethylcyclohexanols (%)	1 max	0.3
Isophorone (%)	0.4 max	0.08
Acid value/mg KOH g^{-1}	0.1 max	0.08[a]

[a] Value measured after discharge of dissolved CO_2, corresponding value before discharge was 8.

in the case of TMCH, SCF technology has eliminated the need for any downstream purification of the product.

Conclusion

The first phase of our collaboration has reached a successful conclusion. The reaction methodology developed in the laboratory has been successfully scaled up to a commercial scale. The academic and industrial partners have generated appropriate outcomes in the form of publications and patents respectively. At the same time there has been a physical transfer of Green Chemistry know-how from university to industry; apart from M.G. Hitzler, all of the post-docs and students sponsored by Thomas Swan, have joined the company after completing their work at Nottingham. Last year Thomas Swan & Co. Ltd. were nominated as one of the top 20 most innovative speciality chemical companies in the world[39] and the work at Nottingham has been recognised by the awarding of an RSC Interdisciplinary Award (MP). In January 2003, the Nottingham-Thomas Swan & Co. research teams won first prize in the

Industrial Innovation Team Award of the Industrial Affairs Division of the Royal Society of Chemistry for their work on 'developing production scale chemistry in supercritical carbon dioxide'.

Overall, we believe not only that our collaboration has been scientifically rewarding to the participants but also that we have demonstrated what can be achieved by a committed academic/industrial partnership. However, the most exciting phase is just beginning. The technology works; now we have to demonstrate whether it is commercially competitive. Such demonstrations are vital to the future of Green Chemistry. Manufacturers will not adopt new, cleaner technologies unless they also provide genuine commercial advantages.

References

1 M. Poliakoff, J. M. Fitzpatrick, T. R. Farren and P. T. Anastas, *Science*, 2002, **297**, 807.
2 J. M. DeSimone, *Science*, 2002, **297**, 799.
3 W. Leitner and P. G. Jessop, *Chemical synthesis using supercritical fluids*, Wiley-VCH, Weinheim, 1999.
4 M. A. McHugh and V. J. Krukonis, *Supercritical fluid extraction: principles and practice*, Butterworth-Heinemann, Boston, MA, 1994.
5 R. K. Upmacis, M. Poliakoff and J. J. Turner, *J. Am. Chem. Soc.*, 1986, **108**, 3645.
6 J. A. Darr and M. Poliakoff, *Chem. Rev.*, 1999, **99**, 495.
7 S. M. Howdle, M. A. Healy and M. Poliakoff, *J. Am. Chem. Soc.*, 1990, **112**, 4804.
8 P. G. Jessop, T. Ikariya and R. Noyori, *Nature*, 1994, **368**, 231.
9 M. Härröd, M.-B. Macher, J. Högberg and P. Møller, *Proceedings of the 4th Conference on Supercritical Fluids and Their Applications*, Capri, Italy, 1997, p. 319.
10 J. A. Banister, A. I. Cooper, S. M. Howdle, M. Jobling and M. Poliakoff, *Organometallics*, 1996, **15**, 1804.
11 J. A. Banister, S. M. Howdle and M. Poliakoff, *J. Chem. Soc., Chem. Commun.*, 1993, 1814.
12 J. A. Banister, P. D. Lee and M. Poliakoff, *Organometallics*, 1995, **14**, 3876.
13 P. D. Lee, J. L. King, S. Seebald and M. Poliakoff, *Organometallics*, 1998, **17**, 524.
14 D. Bradley, *New Sci.*, 1994, **143**, 32.
15 J. M. DeSimone, E. E. Maury, Y. Z. Menceloglu, J. B. McClain, T. J. Romack and J. R. Combes, *Science*, 1994, **265**, 356.
16 T. Tacke, S. Wieland and P. Panster, *Process Technol. Proc.*, 1996, **12**, 17.
17 B. Minder, T. Mallat, K. H. Pickel, K. Steiner and A. Baiker, *Catal. Lett.*, 1995, **34**, 1.
18 K.-H. Pickel and K. Steiner, *Proceedings of the 3rd International Symposium on Supercritical Fluids*, Strasbourg, France, 1994, p. 25.

19 M. G. Hitzler, F. R. Smail, S. K. Ross and M. Poliakoff, *Org. Proc. Res. Dev.*, 1998, **2**, 137.
20 M. G. Hitzler and M. Poliakoff, *Chem. Commun.*, 1997, 1667.
21 M. Härröd and P. Møller, *Process Technol Proc.*, 1996, **12**, 43.
22 A. Bertucco, P. Canu, L. Devetta and A. G. Zwahlen, *Ind. Eng. Chem. Res.*, 1997, **36**, 2626.
23 M. Poliakoff, N. J. Meehan and S. K. Ross, *Chem. Ind.*, 1999, 750.
24 M. G. Hitzler, F. R. Smail, S. K. Ross and M. Poliakoff, *Chem. Commun.*, 1998, 359.
25 F. R. Smail, W. K. Gray, M. G. Hitzler, S. K. Ross and M. Poliakoff, *J. Am. Chem. Soc.*, 1999, **121**, 10711.
26 N. J. Meehan, A. J. Sandee, J. N. H. Reek, P. J. C. Kamer, P. W. M. N. van Leeuwen and M. Poliakoff, *Chem. Commun.*, 2000, 1497.
27 K. W. Gray, D. N. Carter and M. Poliakoff, unpublished results.
28 See, for example: D. P. Cotrupe, W. E. Wellman and P. E. Burton, Patent No., US 3446850, 1969.
29 K. W. Hutchenson, F. E. Herkes, D. J. Walls, T. K. Das and J. F. Brennecke, *Abstr. Pap. Am. Chem. Soc.*, 2001, **221**, 342.
30 P. T. Anastas and J. Warner, *Green Chemistry Theory and Practice*, Oxford University Press, Oxford, UK, 1998.
31 L. Devetta, A. Giovanzana, P. Canu, A. Bertucco and B. J. Minder, *Catal. Today*, 1999, **48**, 337.
32 M. Härröd, S. Van der Hark and A. Holmqvist, *Proceedings of the 8th Meeting on Supercritical Fluids*, Bordeaux, France, 2002, p. 133.
33 M. Nunes da Ponte, A. Milewska, D. Gourgouillon, D. Chouchi and I. Fonseca, *Proceedings of the 8th Meeting on Supercritical Fluids*, Bordeaux, France, 2002, p. 129.
34 D. Chouchi, D. Gourgouillon, M. Courel, J. Vital and M. Nunes da Ponte, *Ind. Eng. Chem. Res.*, 2001, **40**, 2551.
35 J. Ke, B. X. Han, M. W. George, H. K. Yan and M. Poliakoff, *J. Am. Chem. Soc.*, 2001, **123**, 3661.
36 J. Ke, M. W. George, M. Poliakoff, B. X. Han and H. K. Yan, *J. Phys. Chem. B*, 2002, **106**, 4496.
37 The gas–liquid phase boundary of this system was measured in a variable-volume view cell, which consists of a horizontal cylinder mounted with a sapphire window in the front end. The cell volume is changed by moving a piston placed within the cylinder. A sample, with known composition, was then loaded into the cell; any changes in phase behaviour, as a function of temperature and pressure, were monitored. For further details of the experimental technique employed, see reference 4.
38 M. Härröd, S. Van der Hark, A. Holmqvist and P. Møller, *Chem. Eng. Trans.*, 2002, **2**, 537.
39 *Chemical Specialty*, 2001, Sept./Oct., 25.